REMARKS

The Office Action mailed July 29, 2003 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request entry of the amendments and the timely allowance of the pending claims.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendments. Support for the amendments to the claims can be found throughout the specification as originally filed. For example, support for the amendment to claim 25 and new claim 45 may be found on page 23, line 30 to page 25, line 30; Figures 15a and 15b.

Specification

Applicants acknowledge, with appreciation, the indication made on the Office Action Summary sheet mailed with the Office Actions of March 5, 2003 and June 29, 2003 that the formal drawings filed June 29, 2001 are accepted.

Status of the Claims

Upon entry of the foregoing amendment, claims 25-45 will be pending.

Priority

The Office Action at page 2 indicates that if Applicants desire to make a priority claim based on previously filed copending applications, specific reference to the earlier filed applications must be made and the status of said applications must be indicated. Applicants submit herewith an amendment to the specification updating the status of the applications to which priority is claimed. Entry of the amendment is requested.

The Rejection of Claims 25-27, 30-37, 39 and 42 under 35 U.S.C. § 102(e) as being Allegedly Anticipated by U.S. Patent 6,054,270 to Southern et al.

Claims 25-27, 30-37, 39 and 42 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent 6,054,270 to Southern *et al.*

Applicants respectfully traverse the rejection because the '270 patent does not teach or suggest the limitations present in the claims.

The claims have been amended to include a requirement that the binding affinity be determined of the target sequence to at least one probe comprising a single nucleotide variation of the at least one known core sequence probe. This binding affinity is compared to the binding affinity of the target sequence to the at least one known core sequence probe to thereby detect a mutation in a target nucleic acid sequence versus a known sequence. Respectfully, nothing in the '270 patent teaches or suggests the claimed method.

The '270 patent does not teach the presently claimed method because nowhere in the '270 patent is there any teaching or suggestion of determining binding affinity of at least one probe comprising a single nucleotide variation of a known core sequence probe, known core sequence probes, determining binding affinity or comparing the binding affinity of a target sequence to a known core sequence probe and a single nucleotide variation of the known core sequence probe.

The Office Action at page 5 alleges that the '270 patent teaches a comparison of probes with targets over a temperature range and cites column 10, lines 55-65. The presently amended claims require that binding affinities be determined in steps b and c and then compared in step d. The '270 patent does not teach or suggest anything even remotely similar to this because there is no determination of binding affinity in the '270 patent and there is no quantification of these values taught anywhere in the '270 patent. Neither is there any teaching of probes comprising a single nucleotide variation of a known core sequence probe.

Applicants emphasize that the '270 patent is expressly directed to eliminating binding between mismatched probes and targets while the instant invention seeks to determine these binding affinities to detect a mutation in a target sequence. There are no binding affinities to compare in the '270 patent because mismatched probes do not bind and they are washed away.

As stated previously, the method of the '270 patent relies on detecting only perfectly matched sequences to targets. Mismatched sequences are washed away and no binding is detected. See, for example column 10, lines 12-13 stating that "[n]o signal was detectable on the patch with the mismatched sequence." See also column 10, lines 59-61 stating "only the perfectly matched 19-mer was stable, all other oligonucleotides had been eluted." See also

column 10, lines 63 to column 11, line 2 stating "[m]ismatches at the end of the oligonucleotides and at internal sites can all be melted under conditions where the perfect duplex remains. Thus we are able to use very stringent hybridisation conditions that eliminate annealing to mismatch sequences or to oligonucleotides differing in length by as little as one base." See also column 11, lines 30-35 stating "mismatches considerably reduced the melting temperatures of the hybrids, and conditions were readily found such that the perfectly matched duplex remained whereas the mismatched duplexes had fully melted." There is no comparison of binding affinities made in the '270 patent because only perfectly matched sequences are detected and mismatches are washed away.

The Office Action also alleges that the '270 patent at column 11, lines 25-30 "does a comparison between the differently matched targets and compares their melting behavior." Applicants respectfully disagree. The cited passage does not teach what is being claimed because the claims require "b) determining the binding affinity of the target sequence to the at least one known core sequence probe; c) determining the binding affinity of the target sequence to at least one probe comprising a single nucleotide variation of the at least one known core sequence probe" and then comparing these binding affinities. This is simply not taught or suggested in the '270 patent.

The Office Action mailed July 29, 2003 repeats on page 4 what appears to be a quote allegedly taken from a portion of the '270 patent and cites the whole document, especially the abstract and Example 3, as the source for the quote. The quote reads:

> " 'array with multiple oligonucleotides including 19mer oligonucleotide compare hybridization affinity against a temperature gradient thereby detecting mismatches.' "

As stated in the response filed on June 5, 2003, Applicants have carefully reviewed the whole '270 patent and are unable to locate this quote anywhere in the patent. In fact, an electronic search of the '270 patent as it exists on the USPTO website fails to locate any recitation of the words "affinity", "affinities" or "gradient" anywhere in the '270 document. Applicants respectfully request again that the Office point to where in the '270 patent any mention or suggestion is made of binding affinity or absolute binding affinity.

Applicants assert the '270 patent does not teach determining binding affinity because the '270 disclosure relies entirely on eliminating binding of mismatched sequences. In marked contrast, the present invention requires determining these affinities. Neither does the '270 patent teach comparison of binding affinities because only perfectly matched sequences are detected and mismatched sequences are washed away. Furthermore, the '270 patent does not teach or suggest known core sequence probes or probes comprising a single nucleotide variation of the at least one known core sequence probe. For these reasons, the '270 patent cannot anticipate the claims. Withdrawal of the rejection is respectfully requested.

The Rejection of Claim 38 under 35 U.S.C. § 103(a) as being Unpatentable over U.S. Patent 6,054,270 to Southern et al. in view of U.S. Patent 5,633,137 to Shuber

The Office Action alleges that the claim 38 is obvious over the combination of the '270 patent and the '137 patent for the reasons *supra* and because the '137 patent discloses ASO probes for detection of mutations in P-53.

Applicants incorporate by reference the comments made above with respect to the '270 patent. Respectfully, the '137 patent does not cure these deficiencies.

The Rejection of Claims 40 and 41 under 35 U.S.C. § 103(a) as being Unpatentable over U.S. Patent 6,054,270 to Southern et al. in view of U.S. Patent 4,965,189 to Owerbach

The Office Action alleges that the claims 40 and 41 are obvious over the combination of the '270 patent and the '189 patent for the reasons *supra* and because the '189 patent discloses probes for detection of mutations in DQ beta gene.

Applicants incorporate by reference the comments made above with respect to the '270 patent. Respectfully, the '189 patent does not cure these deficiencies.

The Rejection of Claim 43 under 35 U.S.C. § 103(a) as being Unpatentable over U.S. Patent 6,054,270 to Southern et al. in view of U.S. Patent 5,468,613 to Erlich et al.

The Office Action alleges that the claim 43 is obvious over the combination of the '270 patent and the '613 patent for the reasons *supra* and because the '613 patent discloses probe hybridization in forensic analysis.

Applicants incorporate by reference the comments made above with respect to the '270 patent. Respectfully, the '613 patent does not cure these deficiencies.

The Rejection of Claims 28 and 29 under 35 U.S.C. § 103(a) as being Unpatentable over U.S. Patent 6,054,270 to Southern et al. in view of U.S. Patent 5,324,633 to Fodor et al.

The Office Action alleges that claims 28 and 29 are obvious over the combination of the '270 patent and the '633 patent for the reasons *supra* and because the '633 patent discloses plotting the binding affinity results of fluorescence assays on graph and normalized [sic].

Applicants incorporate by reference the comments made above with respect to the '270 patent. Respectfully, the '633 patent does not cure these deficiencies.

Furthermore, Applicants note that the '633 patent and the present application were commonly assigned or under an obligation to assign at the time of the present invention and therefore, under 35 U.S.C. § 103(c) the '633 patent is not available as a reference. Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the foregoing amendments and response, the Applicants respectfully request withdrawal of the outstanding rejections and early notice of allowance to that effect.

If the Examiner finds that a telephone conference would further prosecution of this application, he is invited to call the undersigned at his convenience.

EXCEPT for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Enrique Longton

Enrique D. Longton
Reg. No. 47,304

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Customer No. 000033522
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, NW
Washington, DC 20004
(202) 739-3000
(202) 739-3101 - fax